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EXAMINER

CHANDRAKUMAR, NIZAL S

ART UNIT

PAPER NUMBER

1625

NOTIFICATION DATE

DELIVERY MODE

10/31/2008

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

DETAILED ACTION

Applicants response filed 09/04/2008 is acknowledged.

Telephone Inquiry

In spite of numerous attempts by the Examiner to explore possible amendments to claims to place the application in condition for allowance, no telephone contact could be established with the Attorney for Applicants James B. Myers.

Claims

Applicants Remarks filed 09/04/2008 line 1 and 2 states

Upon entry of the above amendments this application will contain claims 7-9, 11-20, 23, and 36-39 pending.

However, the amended claims list has claims 7-9, 11-13, 16-17, 36-38, 40-43, 14-15, 18-20, 23 and 39.

Election/Restrictions

Previously withdrawn method claims are rejoined with the allowable compound claims.

Claim Rejections - 35 USC § 112

Previously presented rejections under 35 USC § 112 (second and first paragraph) are withdrawn in light of the amendments to the claims.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14, line 2, the term “or;” is confusing because the formulation comprising ingredient (A1) and the ingredient (C) or the formulation comprising (B1) and the ingredient (C1) is intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claim 14 rejected under 35 U.S.C. 102(b) as being anticipated in the prior art.

The formulation of fluorides (Ingredient (B1)-i) in many tooth-paste formulations.

Fluoride was first added to toothpastes in 1914.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 14-15, 18-20, 23 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is not seen where the instant specification adequately describes the use of the compounds of the invention for the prevention of claimed diseases.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”.

These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working

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examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims,
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims: The claims are drawn to treatment, prevention and amelioration of a variety of diseases therapeutically and prophylactically.

The nature of the invention: The nature of the invention is a method of treatment to alleviate and prevent the pathological effects of many diseases including osteoporosis, psoriasis and cancer.

The state of the prior art: The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). While prior art suggests biochemical link between Vitamin receptor activity and osteoporosis and psoriasis, there

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is nothing in the specification or in the prior art to show that compounds of the instant structural class are useful for the prevention or alleviation of these diseases as well as in the treatment of any type of cancer. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic use of any compound, numerous factors such as dose and routes of administration have major in the treatment of any disease. The specification itself contains information on the unpredictable nature of the art. For instance, on page 32, the specification states that isoflavanoids including genistein at concentrations ($<10^{-10}$ M) enhance rather than inhibit the growth of cancer cells. Hence, in the absence of a showing of the effect of the compounds in the treatment of any and all known diseases, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compounds of the instant case due to the unpredictability of the outcome. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of

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potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to

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thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that.

The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years.

Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

The quantity of experimentation needed: The quantity of experimentation needed is undue. One skilled in the art would need to determine what diseases out of all known diseases mediated by Vitamin D receptor activity would be benefited by the mediation of the compounds and then would further need to determine which of the claimed compounds would provide treatment of the disease.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The quantity of experimentation needed: There is a substantial gap between what is disclosed and what is claimed. The quantity of experimentation needed is undue. One skilled in the art would need to determine what compounds of the several possible structures claimed would have the ability to prevent and alleviate all diseases mediated by Vitamin D receptor. .

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Thus, the specification fails to provide sufficient support of the broad use of the compounds for the treatment for prevention and alleviation of osteoporosis, psoriasis and or cancer. Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Conclusion

Claims 7-9, 11-13, 16-17, 36-38, 40-43 are allowable.

Claims 14-15, 18-20, 23 and 39 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar
/D. Margaret Seaman/

Primary Examiner, Art Unit 1625